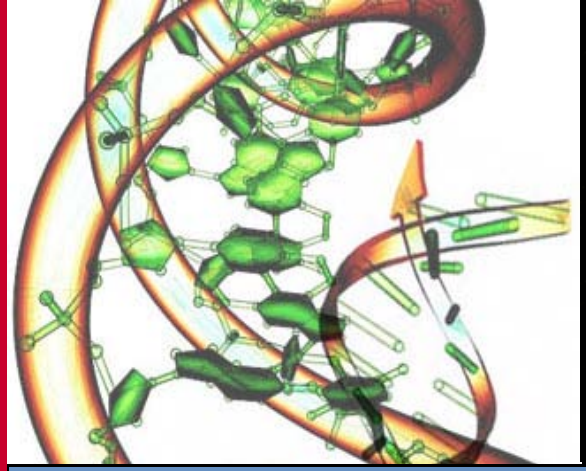

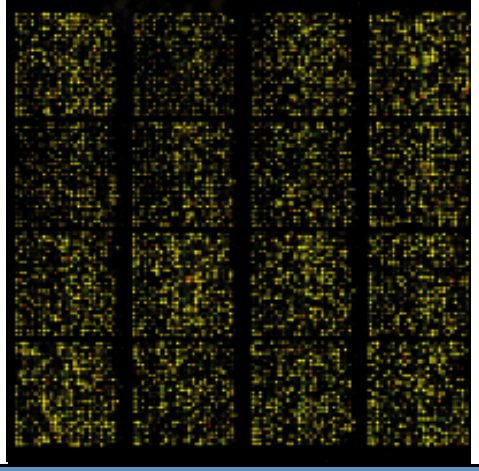

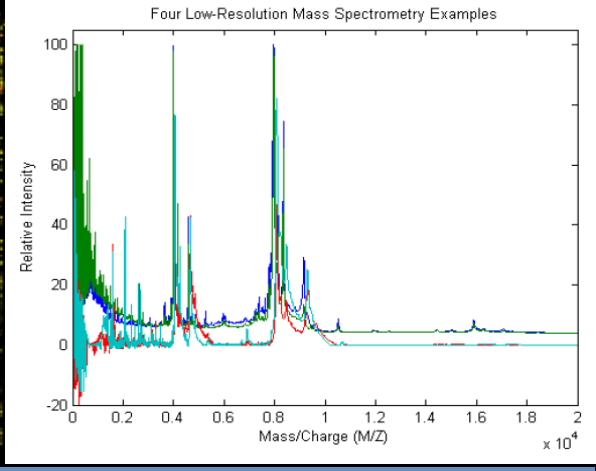

Co-development of diagnostics and therapeutics for cancer

Barbara A. Conley MD
Cancer Diagnosis Program NCI

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Co-development of diagnostics and therapeutics

- Novel therapeutics
- Combinations,
  - radiation and chemotherapy
  - Drug combinations (novel:novel or novel:approved)
- Better use of approved therapeutics

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Objectives

- Definitions
  - Integral, integrated, companion
- Considerations
  - Preclinical research, validation
- Regulations
  - CLIA, FDA

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Promise of Molecularly Guided Treatment of Cancer

- “Get it right the first time”
- Avoid unnecessary toxicity
- Better survival
- Better quality of life

Biomarkers: The Ultimate in Personalized Medicine

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Patient

Disease

Drug

Disease Marker

Biological Markers (Efficacy, Toxicity) N1+N2

Drug Markers

Gene

Conc IC_{95}

Imaging Marker

- Disease present?
- Receptor subtype present?

2D6 cypP450 genotype

- $[Drug]_{plasma(free)}$
- Inhibitory concentration 90%

- PET, MRI,..
- Physical direct evidence for change

- Cell, protein, antibody, small MW chemical, physical measure
- linked to endpoint outcome for efficacy or toxicity
- Prognostic? Predictive?

Modified from J Woodcock, FDA 2006

Or development & therapeutic nightmare?

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Research Assays

- Many “biomarkers” are developed in research labs
- Not very many tests developed in research labs “make it” into clinical use

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Why are successful biomarker studies uncommon?

- Biological heterogeneity
  - Cellular, tumor, patient
- Assay variability
  - Within assay, between assays
- Specimen variability
- Platform biases
- Effect size

A lot of "noise" that blurs marker and outcome correlation and validation

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The Diagnostic is an important part of the treatment!

- The diagnostic should:
  - Be accurate, reproducible in tissues relevant in the clinical setting
  - Inform about the likelihood of the patient's reaction to the treatment
  - Be specific for that treatment
  - Demonstrate *Clinical Utility*

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Research to practice

- Ensure that assays used in clinical trials can be rapidly translated to clinical practice
- Adhere to regulations for assays that are intended to guide clinical decisions
- Optimal use of precious tissue specimens

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Definitions: Validation and Clinical Utility

- *Analytical performance (analytical validity):* how accurately the test detects the analyte(s) of interest
- *Clinical Validity*: How well does the assay result correlate with outcome?
- *Clinical Utility*: How does use of the assay improve outcome?

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Definitions

- *Integral assay*
  - Done on all subjects
  - Used to assign treatment, select subjects or stratify
- *Integrated assay*
  - Done on all subjects
  - Results not used to direct treatment
- *Companion diagnostic*
  - Diagnostic developed to identify patients who are appropriate for treatment with a given (usually novel) drug

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Considerations

- Defining the intended use of the assay:
  - clinical need and
  - competitive existing assays
- Analytical performance: how accurate does the assay need to be?
- Clinical validity: how well does the test relate to the outcome of interest?
- Assessing clinical utility and addressing regulatory issues

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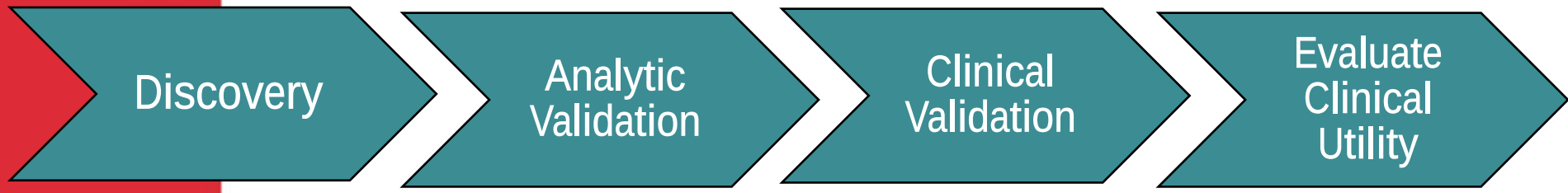
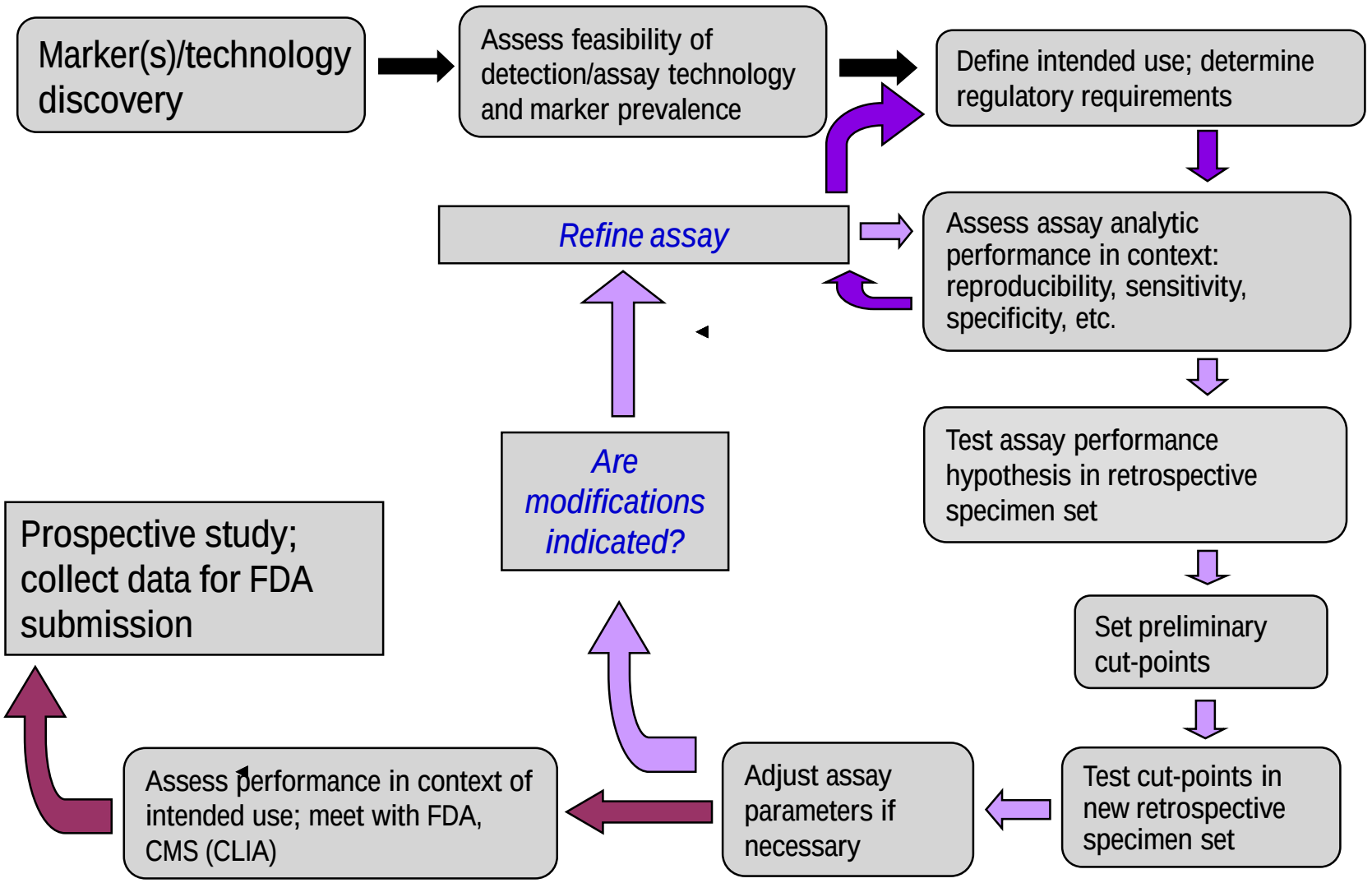
Biomarker to Assay Pipeline



MARKER ASSAY DEVELOPMENT PROCESS



Analytical Validation: Consider

- Sample characteristics
- Positive and negative controls
- Rationale for interfering substances studied
- Analyte (entity)
- Spike-in amounts
- Matrices used for dilution experiments
- Sensitivity/specificity rates over the range of test samples considered
- Calibration/dilution curves

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Needed information

- Assay Protocol (locked down)
- Conditions
- What factors were varied
- Summary metrics, including SD, CV
- Perform precision measurements near clinically important assay values

  (i.e. cut-points)

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Integral assay: Initial development

- Biologic rationale
- Correlates with outcome
- Prevalence
- Magnitude fosters decision
- Analytical validation
- Clinical Validation

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Clinical Utility

DEFINE desired utility of the marker/assay

- Magnitude of the outcome or treatment effects for a "positive" assay must be sufficiently different from "negative" assay so that clinician or patient would accept different treatment strategies for the two groups

Estimates of that magnitude must be reliable

Adapted from Simon R, Paik S, Hayes DF, JNCI 101(21): 1446, 2009

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Types of Clinical Studies

Retrospective Analyses Designs

- Hypothesis generation studies
  - Retrospective analyses based on convenience samples
- Prospective/retrospective designs

Prospective Designs

- Marker by treatment interaction designs (biomarker stratified design)
- Adaptive analysis designs
- Biomarker-strategy designs
- Sequential testing strategy designs
- Hybrid designs

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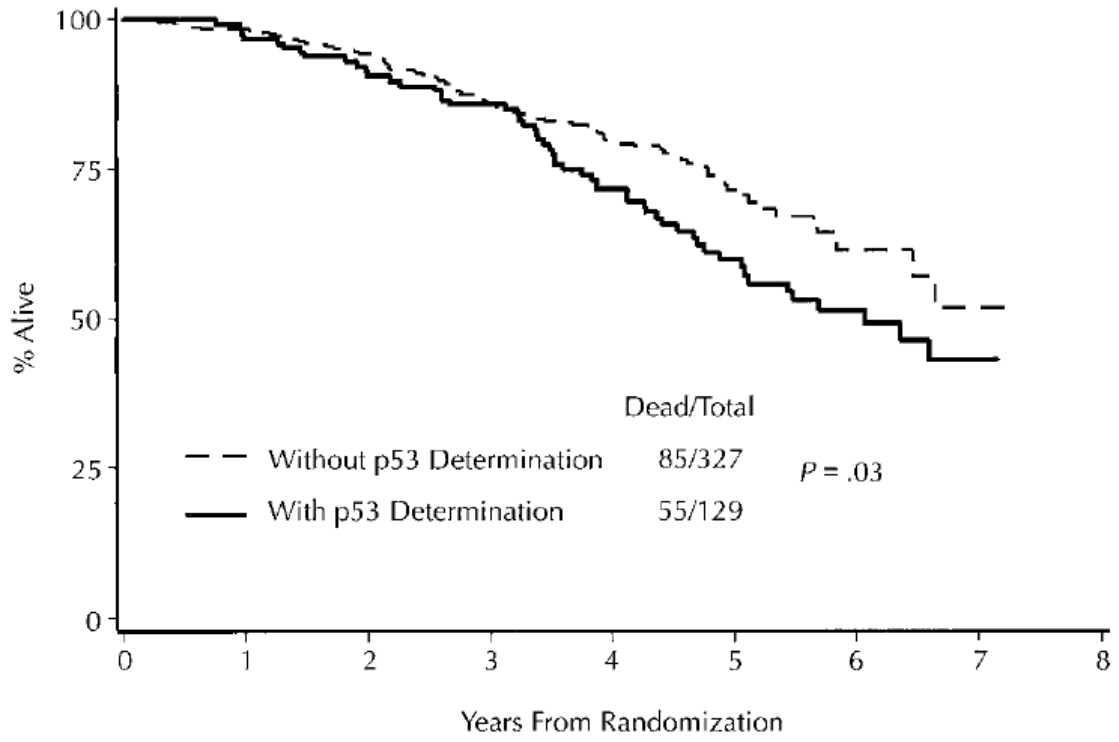
Retrospective Analysis with Incomplete Specimen Collection

- The survival of those patients who had a p53 determined on their tumor was statistically worse than those without a p53 determination (*P* = .03) regardless of the actual p53 assay result.



Data from Grignon et al. J Natl Cancer Inst. 1997;89:158–165.
Figure from Pajak et al. Arch Pathol Lab Med. 2000;124:1011–1015

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Validation: Clinical utility

- Intended clinical use clearly specified
- Specimen processing, assay methods, and data processing methods *as to be used in clinical setting (one patient at a time)*
- Clinically meaningful degree of benefit (more than a significant p-value!)
- What is the value added?
  - Outperforms or adds to existing tests
  - Performs equivalently but more easily, less expensively, or less invasively than existing tests

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Potential Clinical Utility

- Identify **prognostic** groups
  - Who can avoid treatment?
  - "Drivers" of prognostic groups can suggest new therapeutic targets
- Define which patients will benefit from particular treatments (**predictive**)
  - Selection criterion for novel agents
  - Optimal combinations of standard treatments

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Potential Clinical Utility

- Define which patients are likely to develop serious toxicities from particular treatments ("negative predictive")
  - Need alternative, acceptable treatment
- Understand biological mechanism and monitor for treatment success or failure
  - Requires repeat specimens from patient

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Discovery: Serum proteomic profile to classify NSCLC for outcome with EGFR-TKIs

- Serum collected from NSCLC patients before treatment with gefitinib or erlotinib
- Analysis by MALDI-MS
- K-nearest neighbor (KNN) algorithm based on 8 distinct m/z features classifies into good or poor outcome
- Training set: n=139 NSCLC patients total from 3 cohorts who received gefitinib
- Validation cohorts:
  - "Italian B": n=67 sequential patients, late-stage or recurrent NSCLC treated with single-agent gefitinib
  - ECOG 3503: n=96 advanced NSCLC patients treated with first-line erlotinib on single arm Phase II study

Taguchi et al, *JNCI* 2007

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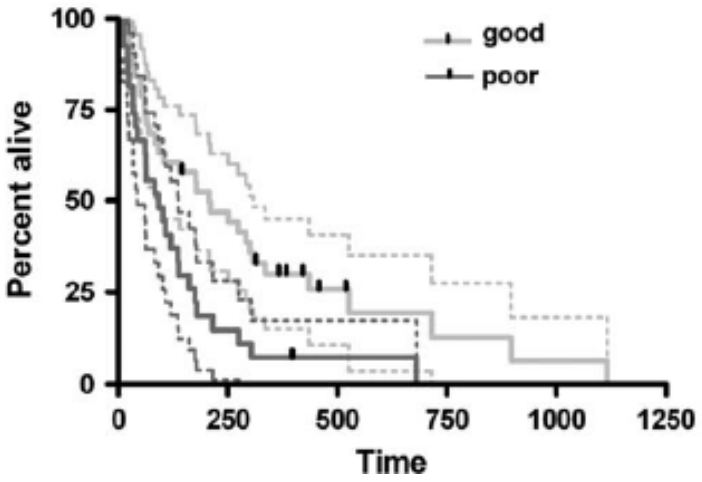
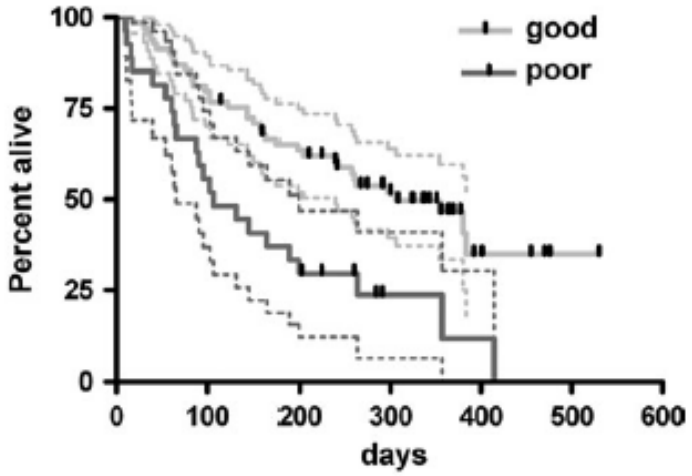
Clinical Validation: Serum proteomic profile to classify NSCLC for outcome with EGFR-TKIs

- Validation results for patients treated with EGFR-TKIs



"Italian B": n=67 sequential patients, late-stage or recurrent NSCLC treated with single-agent gefitinib
HR=0.50, 95% CI=(0.24,0.78), p=0.0054
Median OS
Good: 207 days Poor: 92 days



ECOG 3503: n=96 advanced NSCLC patients treated with first-line erlotinib on single arm Phase II study
HR=0.4, 95% CI=(0.24,0.70), p<0.001
Median OS
Good: 306 mos. Poor: 107 mos.

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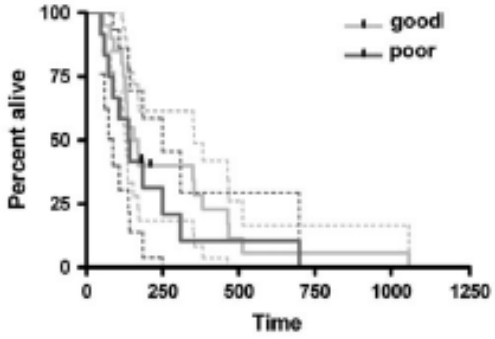
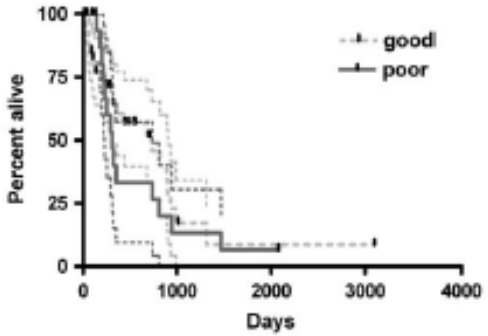
Predictive or Prognostic? Serum proteomic profile to classify NSCLC for outcome

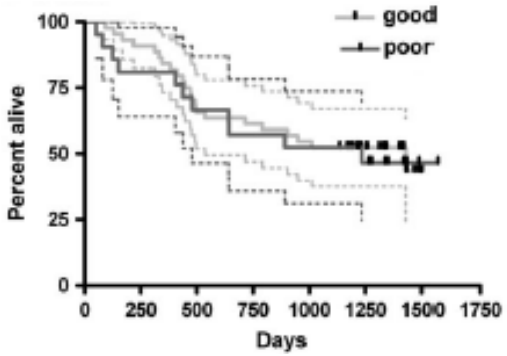
Does the profile also separate by outcome patients who did NOT receive EGFR-TKIs (control cohorts)?



"Italian C": n=32 patients, stage IIIA-IV NSCLC treated with second-line chemotherapy
HR=0.74, 95% CI=(0.33,1.6), p=0.42



"VU": n=61 patients, advanced NSCLC treated with second-line chemotherapy
HR=0.81, 95% CI=(0.4,1.6), p=0.54



"Polish": n=65 patients, stage IA-IIB NSCLC treated with second-line chemotherapy
HR=0.90, 95% CI=(0.43,1.89), p=0.79

Lessons Learned: Serum proteomic profile to classify NSCLC for outcome

- Does non-significance in control cohorts mean profile is *predictive*, or is lack of prognostic effect due to
  - Small sample size (lack of power)
  - Differences in patient characteristics
  - Differences in specimen handling
- Limited availability of retrospective serum sample collections from randomized trials
- Changing targeted therapy landscape (EGFR mutation & EGFR-TKIs) may make it difficult to answer the original predictive question in a new trial
- Inter-lab reproducibility is achievable for proteomic assays

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Regulatory Considerations

- CLIA
- FDA
  - PMA
  - 510k
  - Investigational Device Exemption (IDE)

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CLIA

- Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed.
- CLIA is user fee funded
- final CLIA regulations were published on February 28, 1992 and are based on the complexity of the test method

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Three categories of tests

- waived complexity
- moderate complexity
- high complexity

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CLIA Application

- Describes characteristics of laboratory examinations and other procedures
  - Number and types of procedures/exams
  - Methodologies employed
  - Qualifications of personnel (education, background, training, experience) of supervisors and personnel performing procedures

CLIA: Proficiency testing

- For each examination or procedure for which laboratory received Certificate, except if proficiency test cannot be developed
- Usually quarterly, but not less than twice per year
- No assessment of inter-laboratory consistency

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Device Classification - FDA

- 510K: A device may not be marketed in the U.S. until the submitter receives a letter declaring the device substantially equivalent
- Premarket Approval (PMA) regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer

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510k substantially equivalent

- New device is at least as safe and effective as the predicate
  - same intended use **and**
  - same technological characteristics
    or
  - same intended use **and**
  - different technological characteristics and
    - does not raise new questions of safety and effectiveness; **and**
    - demonstrates that the device is at least as safe and effective as the legally marketed device.

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Premarket Approval

- Scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.
  - support or sustain human life,
  - are of substantial importance in preventing impairment of human health, or
  - which present a potential, unreasonable risk of illness or injury

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Integral Assays –When to consider IDE

- Non-cleared assay used for selection, assignment, monitoring
- Even if no original or supplemental therapeutic submission is planned
- Even if no IND approval required.
- Evaluate risk, potential gain

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IDE: when is device ready to be used in a trial?

- Fully specified device (for purposes of the trial)
- Analytic performance adequately assessed
- Pre-clinical or clinical information justifies evaluation in patients
- Well-posed question/hypothesis
- Benefit > Harm (likely)

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Specified Device

- Analyte(s)
- Reagents, equipment, methods, software
- Performance specifications (including pre-analytical)
- Instructions for use

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Analytical Performance

- Pre-analytical issues
- Precision
- Reproducibility
- Interferences/specificity
- Robustness/sensitivity
- Cut-off assignment
- Others (e.g. model)
- Success criteria (aligned with clinical use)

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Justifying human subject participation

- “window of opportunity” equipoise
- Device’s relevance to the opportunity
- Design, bench testing
- Animal testing
- Previous clinical testing

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Protocol

- Well identified question/hypothesis
- Well-defined population, trial procedures, outcome measures
- Pre-specified statistical analysis plan; success criteria
- Prospects for applying the answers effectively

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Conclusions

- Biologic discoveries and new targeted therapies drive the agenda for personalized medicine
- Proper consideration needs to be given to the reliability and robustness of the diagnostic assay
- Often difficult to assess prognostic from predictive without prospective trial
- Regulatory issues should be considered early